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Sleep-wake cycle disturbances in elderly acute general medical inpatients: Longitudinal relationship to delirium and dementia

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Abstract

Introduction: Sleep disturbances in elderly medical inpatients are common, but their relationship to delirium and dementia has not been studied.

Methods: Sleep and delirium status were assessed daily for a week in 145 consecutive newly admitted elderly acute general hospital patients using the Delirium Rating Scale-Revised-98 (DRS-R98), Diagnostic and Statistical Manual 5, and Richards-Campbell Sleep Quality Scale measures. The longitudinal relationship between DRS-R98 and Richards-Campbell Sleep Quality Scale sleep scores and delirium, also with dementia as a covariate, was evaluated using generalized estimating equation logistic regression.

Results: The cohort was divided into delirium only, dementia only, comorbid delirium-dementia, and no-delirium/no-dementia subgroups. Mean age of total group was 80 ± 6.3, 48% were female, and 31 (21%) had dementia, 29 had delirium at admission (20%), and 27 (18.5%) experienced incident delirium. Mild sleep disturbance (DRS-R98 sleep item score ≥1) occurred for at least 1 day in all groups, whereas moderate sleep disturbance (score ≥2) occurred in significantly more of the prevalent delirium-only (81%; $n = 17$) cases than incident delirium-only (46%; $n = 13$) cases ($P < .001$). There were more cases with DRS-R98 sleep item scores ≥2 ($P < .001$) in the delirium-only group compared with the other subgroups. Severity of sleep-wake cycle disturbance over time was significantly associated with Diagnostic and Statistical Manual 5 delirium status but not with age, sex, or dementia ($P < .001$).

Conclusions: Observer-rated more severe sleep-wake cycle disturbances are highly associated with delirium irrespective of dementia status, consistent with being a core feature of delirium. Monitoring for altered sleep-wake cycle patterns may be a simple way to improve delirium detection.

Keywords: Dementia; Delirium; Sleep disturbance detection; Elder care medicine

1. Introduction

The sleep-wake cycle is a complex phenomenon driven by the circadian system through a variety of neuroendocrine processes. Impaired sleep-wake cycle is associated with deficits

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in cognition [1–3]. Disturbances in sleep-wake cycle and cognition are common in older medical inpatients, but the relationship is not fully understood. In addition, sleep disturbances are common in mild and major neurocognitive disorders such as dementias and delirium [4–7]. As such, there is a strong relationship between sleep and neurocognitive disorders, with these entities each impacted on by the circadian timing system [8–10]. Delirium is a complex neuropsychiatric syndrome indicative of acutely impaired consciousness and associated with a number of adverse clinical outcomes in hospitalized older people, including increased risk of mortality [11]. It is a common occurrence in the acute hospital setting, with a point prevalence of approximately 20% [12] and can be complicated by the presence of other neuropsychiatric conditions, such as depression and dementia [12,13]. Delirium phenomenology has been divided into three core domains: circadian, general cognitive, and higher order thinking. Sleep disturbances are part of the circadian domain, along with motor activity disturbances [14]. Sleep disturbances can present as insomnia, sleep fragmentation, daytime somnolence, and reversal of sleep-wake phases [15] and are measurable using the Delirium Rating Scale-Revised-98 (DRS-R98).

Sleep disturbances have been reported in up to two-thirds of patients with Alzheimer's disease, whereas other dementias, such as vascular and Lewy body dementia, have reported such disturbances in up to 90% of patients [16]. In the hospital setting, sleep and cognition can be also affected by environmental factors, psychoactive medications, surgery, age, pain, and other medical and neuropsychiatric conditions.

The relationship between sleep-wake cycle disturbances and delirium in elderly general medical inpatients suggests that they could be a useful clinical indicator of possible delirium. Hence, the purpose of this study was (1) to prospectively evaluate the longitudinal relationship between delirium and sleep-wake cycle disturbances (observer and subjectively rated) in newly admitted nonselective elderly general medical patients, and (2) to explore how these patterns relate to delirium episode severity, specifically controlling for dementia as a potential confounder.

2. Methods

2.1. Study design

We conducted a prospective study of older medical inpatients admitted through the emergency department of a tertiary referral acute hospital in Cork city, Ireland (Cork University Hospital). The study was conducted between August 2012 and August 2013. Patients were screened for study inclusion within 36 hours of admission. Initial criteria for patient exclusion were (1) requiring specialist intervention (e.g., hematology, oncology, and patients admitted to the intensive care unit), (2) patients deemed too unwell to participate (e.g., actively dying), and (3) refusal to participate. After recruitment, nondelirious patients were also excluded if they were discharged within 3 days of admission (as we could not confidently rule out the development of delirium within the first week of admission in these patients).

2.2. Ethical approval

The procedures and rationale for the study were explained to all patients but because many patients had cognitive impairment at entry to the study, it was presumed that most were not capable of giving informed written consent. Because of the noninvasive nature of the study, Cork Research Ethics Committee approval was given to augment patient assent with proxy consent from next of kin (where possible) or a responsible caregiver in accordance with the Helsinki Guidelines for Medical Research involving human subjects [17].

2.3. Medication data

All medications (regular and required doses) prescribed for each patient were documented by a senior research fellow (N.O.R.) in geriatric medicine at each daily assessment of delirium phenomenology. The use of psychoactive agents was a specific focus, especially the use of antipsychotics, opioids, benzodiazepines, psychostimulants, and corticosteroids [18]. Dose equivalents for more than 24 hours before assessment were calculated for each drug class according to accepted conversion rates (i.e., antipsychotics in chlorpromazine equivalents; opioids in morphine equivalents; benzodiazepines in diazepam equivalents; corticosteroids in prednisolone equivalents) [19].

2.4. Sleep assessment

Sleep was assessed at baseline and daily thereafter for a week. Two approaches were applied to measure sleep patterns: (1) the DRS-R98 item for sleep-wake cycle disturbances (item #1), which is a clinician-rated anchored clinical assessment of sleep-wake cycle disturbance, and (2) the Richards-Campbell Sleep Questionnaire (RCSQ), which is a patient self-report scale assessing subjective quality of sleep. These assessments were done separately. The clinician-rated anchored clinical assessment of sleep-wake cycle disturbance was conducted by a specially trained research fellow (N.O.R.) in geriatric medicine. The subjective psychometric assessment was conducted by a specially trained neuroscientist (J.F.) and was done in the early morning to optimize patient's recollection and representation of their sleep quality.

Sleep-wake cycle disturbance severity was rated daily using DRS-R98 item #1. It assesses sleep-wake cycle disturbances on a four-point Likert scale described as "no disturbance (0), mild nocturnal sleep disturbance or occasional daytime drowsiness (1), moderate disorganization of sleep-wake cycle evidenced by daytime napping, brief periods of nocturnal awakening (2), and severe disruption of

sleep-wake cycle as evidenced by day-night reversal of sleep-wake cycle or severe circadian fragmentation with multiple periods of sleep and wakefulness or severe sleeplessness (3)." [20].

Sleep quality was measured daily using the RCSQ [20]. This self-rated visual analog scale measures sleep along a 0 to 100 point continuum according to five dimensions: "1. Depth: light sleep (0) to deep sleep (100); 2. Latency of sleep: just never could fall asleep (0) to fell asleep almost immediately (100); 3. Number of awakenings: awake all night long (0) to awake very little (100); 4. Return to sleep: couldn't get back to sleep (0) to got back to sleep immediately (100); and 5. Sleep quality of the previous night: a bad night's sleep (0) to a good night's sleep (100)." For each dimension the patient indicated their score along a 100-mm line. The total sleep score reflects the average of these five domains, ranging from 0 (poorest possible sleep) to 100 (optimum sleep). For daily ratings the patients were guided by clear instructions as how to rate their sleep on the visual analog scale. Sleep was not organized into discrete categories according to sleep rating scores. The instrument has been validated against polysomnography in intensive care unit patients [21].

2.5. Delirium assessment

A systematic algorithm-based method was used daily to identify Diagnostic and Statistical Manual 5 (DSM-5) defined delirium as published previously by our research group [22–24]. The algorithm method uses a checklist to ensure capture of all available sources of information including clinical interview of patient, use of validated bedside tests of cognition, collateral interview with nursing staff, and collateral history from family members. This algorithm-based method was rated independently of the DRS-R98. Consensus discussion was used to apply diagnosis in borderline cases.

Delirium phenomenology was assessed for all patients daily (N.O.R.) throughout the study using the DRS-R98 [20]. The DRS-R98 is a well-validated and widely used instrument to measure symptom profile and severity in delirium, and rate symptoms up to and including the preceding 24-hour period, using all sources of information. It is a 16-item clinician-rated scale with 13 severity items and three diagnostic items, producing Total and Severity Scale scores. Item rating levels (0–3) are anchored by phenomenological text descriptions and higher scores indicate more severe delirium. It has high inter-rater reliability, validity, sensitivity, and specificity for distinguishing delirium in mixed neuropsychiatric populations [20].

The Delirium Motor Subtype Scale (DMSS) [25] is a scale comprising 13 (five hyperactive and eight hypoactive) symptoms selected according to their reflection of motor phenomenology, relative specificity for delirium relative to controls, and demonstrated correlation with independent and objective measures of motor behavior [25]. The DMSS can be rated by any healthcare professional familiar to the clinical presentation of delirium. Scoring requires at least two features to be present from either the hyperactive or hypoactive list to meet subtype criteria. Patients meeting both hyperactive and hypoactive criteria are deemed mixed subtype, whereas patients meeting neither criteria are labeled "no subtype."

The delirium etiology checklist was used to determine the degree of attribution of causative factors to cases of delirium [26]. The delirium etiology checklist has 12 categories: drug intoxication, drug withdrawal, metabolic/endocrine disturbance, traumatic brain injury, seizures, infection (intracranial), infection (systemic), neoplasm (intracranial), neoplasm (systemic), cerebrovascular, organ insufficiency, other central nervous system, and other systemic and is rated on a five-point scale ranging from "ruled out/not present/not relevant (0)" to "definite cause (4)". Etiologic ratings of "definite, probable, and possible," that is, scores $\geq$2 were listed as contributory to delirium for the purposes of this study. This method provides specifically relevant information to cases of delirium rather than simply listing the current medical conditions at the time of assessment [27].

2.6. Dementia assessment

For all patients, medical case notes were reviewed for a diagnosis of pre-existing cognitive impairment or dementia. In addition, short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [28] was used to assess preadmission cognitive status at the initial assessment. This 16-item scale was scored by interviewing a caregiver or close relative who knew the patient. A mean item cutoff score $\geq$3.5 was used to diagnose probable dementia [28]. Consensus discussion was used to apply diagnosis in patients whose dementia status required confirmation and clarity. In the absence of an available informant, patients were considered not to have dementia if they scored $\geq$27/30 on the standardized Mini-Mental State Examination (sMMSE) [29]. A previous study has shown that only 2% of older inpatients with dementia are missed using this cutoff [30].

2.7. Depression assessment

The short form of the Geriatric Depression Scale was used to screen for depression status at the initial assessment. This 15-item scale was rated by a trained interviewer; a total score $\geq$5 indicated possible depression [31].

2.8. Statistical analysis

Statistical analysis was conducted using the SPSS-19 package (IBM, Armonk, NY, USA). Continuous variables are reported as the means $\pm$ standard deviation, whereas categorical variables are reported as counts and percentages. Analysis of variance with post hoc Tukey tests was used for group comparisons. Spearman's rho was used to examine the correlation between DRS-R98 and RCSQ ratings. The generalized estimating equation (GEE) method analyzed

repeated measures of scores for DRS-R98 sleep-wake cycle item #1 (0–3) and RCSQ quality of sleep (0–100) using data from every rating day [32]. GEE functions as a form of logistic regression whereby each patient's score is included along with a measure for intraindividual correlations. This takes into account that the observations within a subject are interdependent. Also, it has relaxed assumptions about the distribution of data.

3. Results

3.1. Demographic and general clinical characteristics

Of 277 patients initially assessed, 145 (52%) were included and 132 (48%) were excluded from the study. The reasons for exclusion were refusal to participate ($n = 65$), terminally unwell ($n = 32$), early discharge from hospital ($n = 28$), and patients requiring nongeneral medical treatment ($n = 7$). In 6% of cases ($n = 9$) there was no IQCODE and a cutoff of ≥27/30 on sMMSE was used to rule out dementia. The number of cases of patients with no IQCODE and sMMSE of 26/30 or less was 2.7% ($n = 4$). For such patients, where IQCODE collateral history was unavailable, the person was excluded from any assignment of dementia status. A random sample of 10 early discharges from a total of 28 had IQCODEs completed with a median score of 3.13 (range 3.0–3.21; interquartile range [IQR] 0.1864). The mean age was 80 years (±6.3; age range 70–94) and 69 (48%) were female. Only six patients were administered one or more classes of psychotropic or pain medication during the week of observation: benzodiazepines and hypnotics ($n = 8$), antipsychotics ($n = 3$), antidepressants ($n = 2$), and opioids ($n = 6$). Six patients (4%) were depressed at admission. The cohort underwent a total of 661 assessments for more than the 7-day-rating period, ranging from 145 assessments on assessment day 1, to 51 on assessment day 7.

Patients were divided into diagnostic groups for delirium-only ($n = 34$; 21 prevalent at admission and 11 incident), dementia-only ($n = 22$), comorbid delirium-dementia ($n = 17$), and no-delirium/no-dementia (NDND) ($n = 93$) according to DSM-5 criteria. The overall prevalence of delirium at admission was 20% ($n = 29$), whereas another 27 patients (18.5%) developed incident delirium. The frequency of motor subtypes according to the DMSS at baseline assessment ($n = 143$) was 47.6% hypoactive ($n = 69$), 4.1% mixed ($n = 6$), 2.8% hyperactive ($n = 4$), and 44.1% no subtype ($n = 64$). The most common underlying etiologic group for the delirium-only cases ($n = 34$) was that of organ insufficiency (27%; $n = 9$) causes, and this was followed by systemic infections (20.5%; $n = 7$) and metabolic/endocrine disturbances (20.5%; $n = 7$). Details of other etiologic causes are shown in Table 1. Among 31 (21%) patients with probable dementia, eight also had prevalent delirium at admission and nine developed incident delirium for a total of 17 (58%) with comorbid delirium-dementia. The mean sMMSE scores for the dementia-only group and the comorbid delirium-dementia group were 21 ± 2 and 22 ± 4, respectively. The median IQCODE scores for delirium motor subtypes were hyperactive = 3.5 (range 3.4–3.6; IQR 0.21), hypoactive = 3.52 (range 3.0–3.55; IQR 0.22), mixed = 3.09 (range 3.0–3.18; IQR 0.180), and no subtype = 3.10 (range 3.0–3.2; IQR 0.175).

Table 1
Etiology as per delirium etiology checklist ($n = 34$)

Etiologic groups	% (n)
Drug intoxication	15% ($n = 5$)
Drug withdrawal	0% ($n = 0$)
Metabolic/endocrine disturbance	20.5% ($n = 7$)
Traumatic brain injury	0% ($n = 0$)
Seizures	0% ($n = 0$)
Infection (CNS)	0% ($n = 0$)
Infection (systemic)	20.5% ($n = 7$)
Neoplasm (CNS)	0% ($n = 0$)
Neoplasm (systemic)	0% ($n = 0$)
Cerebrovascular	8% ($n = 3$)
Organ insufficiency	27% ($n = 9$)
Other CNS	3% ($n = 1$)
Other systemic	6% ($n = 2$)

Abbreviation: CNS, central nervous system

Mean DRS-R98 Severity and Total scale scores were significantly different between the delirium-only group ($P < .001$), the comorbid delirium-dementia group ($P < .001$), and the NDND (see Table 2). There was no significant difference between the mean DRS-R98 Severity and Total scores for patients with either prevalent or incident delirium.

3.2. Sleep patterns

Table 2 shows sleep rating results for the DRS-R98 item #1. Sleep disturbance (mean score ≥1) occurred in all diagnostic subgroups. There was a significant difference in DRS-R98 item #1 mean scores between the delirium-only group and the other groups: NDND ($P = .002$), dementia-only group ($P = .008$), and the comorbid delirium-dementia group ($P = .017$). Moderate or greater levels of sleep disturbance (score ≥2) occurred in significantly more of the prevalent (81%; $n = 17$) than incident (46%; $n = 13$) delirium-only cases ($P < .001$).

The dementia-only group had slightly lower mean DRS-R98 sleep item scores (1.05 ± 0.58) than all other groups, but the scores only differed significantly from the delirium-only group ($P = .008$). Most patients with dementia-only (68%; $n = 15$) had mild sleep disturbance (score = 1) and mean sleep disturbance for the NDND group did not differ from the dementia-only group ($P = .491$). The occurrence of a sleep disturbance score ≥1 in the NDND group was 87% ($n = 20$), with most of these cases also being rated as mild sleep disturbance (score = 1) at 69.6% ($n = 16$).

RCSQ ratings (see Table 3) of sleep quality are reported for total scores and each of the five dimensions. There was no significant difference between any of the groups in terms of the RCSQ mean total score or dimension score. The correlation between DRS-R98 sleep item ratings and the total

Table 2
Peak day values for the Revised Delirium Rating Scale-98 (DRS-R98) item #1 (sleep-wake cycle disturbance) according to the presence of delirium and dementia

DRS-R98	Prevalent delirium without dementia (n = 21)	Incident delirium without dementia (n = 13)	Delirium-only (n = 34)	Delirium plus dementia (n = 17)	Dementia-only (n = 22)	No delirium or dementia (n = 93)
Item #1 score	1.52 ± 0.54	1.31 ± 0.53	1.46 ± 0.53	1.10 ± 0.54	1.05 ± 0.58	1.01 ± 0.61
Item #1 = 0	0 (0%)	0 (0%)	0 (0%)	2 (12%)	3 (14%)	3 (13%)
Item #1 = 1	4 (19%)	7 (54%)	11 (32%)	12 (61%)	15 (68%)	16 (69.6%)
Item #1 = 2	17 (81%)	5 (38.3%)	22 (65%)	3 (17%)	4 (18%)	4 (17.4%)
Item #1 = 3	0 (0%)	1 (7.7%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)
Severity scale	13.62 ± 2.91	12.59 ± 2.89	13.14 ± 2.90	10.23 ± 2.43	9.52 ± 2.93	6.71 ± 3.03
Total scale	17.86 ± 3.87	16.05 ± 3.02	16.89 ± 3.56	11.65 ± 2.77	10.09 ± 2.89	7.86 ± 3.90

NOTE. Data are expressed as the mean ± standard deviation or as frequencies n (%).

RCSQ score was low for the overall population ($r = -0.06$), as well as for those who had prevalent delirium ($r = -0.27$), those who subsequently developed incident delirium ($r = -0.19$), and for those who did not develop delirium during the study ($r = 0.08$).

3.3. Relationship between sleep status and other clinical variables over time

Table 4 shows a GEE model of the relationship across all assessments between sleep-wake cycle disturbance (DRS-R98 item #1 score) and other demographic and clinical characteristics. Of note, severity of sleep-wake cycle disturbance over time was significantly associated with DSM-5 delirium status but not age, sex, dementia, or depression status. A similar analysis was performed to examine for variables associated over time with sleep quality according to total scores on the RCSQ scale (see Table 4). In contrast to the findings for the DRS-R98, sleep quality was significantly associated with depression status rather than any other clinical or demographic variables. However, the number of patients with depression is low, which makes this finding not entirely reliable.

3.4. DRS-R98 sleep item ratings and prediction of DSM-5 delirium status

Using ratings only on days for which they met delirium diagnostic criteria, 100% of 116 cases with delirium scored ≥1 and 81 (70%) scored ≥2 on the DRS-R98 item for sleep-wake cycle disturbance. Examining DRS-R98 item #1 ratings' prediction of DSM-5 detected delirium, when using a cutoff ≥1, the sensitivity was 80%, specificity was 74%, positive predictive value (PPV) was 66%, and negative predictive value (NPV) was 74%. When a cutoff ≥2 was applied, sensitivity was 77%, specificity was 92%, with a 52% PPV and 79% NPV.

4. Discussion

Sleep-wake cycle disturbances have been widely appreciated as key symptoms of delirium for decades [33]. More recent studies have highlighted the frequency of disturbances of sleep-wake cycle in delirium and suggested that although milder disturbances are very common in hospitalized patients, more severe disturbances are indicative of delirium [34,35]. Therefore, we examined sleep-wake cycle patterns in 145 acute older medical general hospital inpatients using both subjective patient self-ratings and clinician-rated assessments and their relationship to delirium. Unlike prior studies, we conducted a longitudinal data study and analyzed using GEE and also addressed the relationships between DSM-5 diagnosed delirium and dementia with sleep-wake cycle disturbances.

As expected, pre-existing dementia was evident in more than one-fifth of patients, whereas 20% had prevalent delirium at admission and almost a further 20% developed incident delirium during the first week of hospitalization. Overall, slightly more than 20% of all daily DSM-5 assessments were positive for delirium, and this is in keeping with other studies of older general hospital inpatients where as a general rule of thumb approximately one in five experience

Table 3
Peak day sleep ratings using the Richards-Campbell Sleep Questionnaire (RCSQ) according to the presence of delirium or dementia

RCSQ	Prevalent delirium without dementia (n = 21)	Incident delirium without dementia (n = 13)	Delirium-only (n = 34)	Delirium plus dementia (n = 17)	Dementia-only (n = 22)	No delirium or dementia (n = 93)
Latency	66.7 ± 9.5	65.4 ± 9.7	65.9 ± 9.6	65.1 ± 9.3	64.3 ± 9.2	65.2 ± 8.9
Depth	65.9 ± 5.3	64.7 ± 8.7	65.1 ± 6.7	66.3 ± 8.6	67.1 ± 9.8	68.9 ± 4.8
Number of awakenings	66.7 ± 5.7	68 ± 7.7	67.5 ± 6.5	65.3 ± 6.5	63.9 ± 6.6	65.9 ± 6.5
Quality	67.7 ± 6.9	63.9 ± 7.6	65.3 ± 7.3	64.9 ± 7.4	64.6 ± 7.7	64.8 ± 8.2
Ease of return to sleep	68.5 ± 5.4	66.3 ± 7.6	67.2 ± 6.6	66.9 ± 6.9	66.8 ± 7.2	63.9 ± 6.4
Total score	65.8 ± 4.8	66.4 ± 5.0	66.3 ± 4.9	65.7 ± 5.1	65.1 ± 5.4	64.5 ± 5.2

NOTE. Values are expressed as the means ± standard deviations. There were no significant differences among the groups on any variable.

Table 4
Generalized estimating equation model for sleep-wake cycle ratings using Revised Delirium Rating Scale-98 (DRS-R98) item #1 score and Richards-Campbell Sleep Questionnaire (RCSQ) total score according to demographic (age, sex) and neuropsychiatric disorder status (delirium, depression, and dementia)

Factors	Coefficient	Standard error	*P* value	Wald χ^2	*df*	95% Confidence interval
DRS-R98 Item #1						
Delirium	−0.54	0.08	<.001	48.9	1	−0.69 to −0.39
Dementia	0.05	0.08	.55	0.36	1	−0.10 to 0.19
Depression	−0.08	0.14	.5	0.33	1	−0.35 to 0.19
Age	0.01	0.00	.8	0.06	1	−0.009 to 0.012
Sex	0.02	0.06	.8	0.06	1	−0.10 to 0.13
Constant	1.51	0.49	.002	9.7	1	0.56–2.47
RCSQ						
Delirium	−1.23	0.62	.23	3.89	1	−0.35 to 0.19
Dementia	−0.43	0.63	.50	0.47	1	−1.66 to 0.80
Depression	0.58	0.49	.04	1.45	1	−1.54 to 0.37
Age	0.03	0.04	.40	0.67	1	−0.04 to 0.11
Constant	66.9	3.29	<.001	412.9	1	60.4–73.4

delirium during hospitalization [12,36]. Similar to previous studies, comorbidity between delirium and dementia was common, with almost two-thirds of those with dementia experiencing delirium at some point during the first week of their hospitalization. This comorbidity raises the question of whether sleep-wake cycle disturbances are reflective of delirium even in the context of dementia.

Mild sleep disturbances were very common in this medical inpatient sample, and only eight patients had none. Given that dementia includes sleep-wake cycle impairments, we were surprised that the dementia-only group's mean DRS-R98 item #1 scores were similar to the NDND group. Certainly just being medically ill and in a hospital setting can be associated with some insomnia, suggested by the NDND group ratings. The delirium-only group had more severe sleep-wake cycle impairment on the DRS-R98 than the dementia-only, comorbid delirium-dementia, or NDND groups. In addition, the prevalent delirium group had significantly more severe sleep-wake cycle disturbance than the incident delirium group, although the overall delirium symptom levels on the DRS-R98 total scales were similar, so the difference cannot be attributable to prevalent delirium being more severe overall. There were far fewer cases with DRS-R98 sleep-wake cycle scores of moderate ratings in the dementia or NDND groups, and none had a severe (three points) rating. It is surprising, however, that the sleep ratings in the comorbid delirium-dementia group were not more similar to other delirium subgroups (i.e., patients with prevalent or incident delirium), as the literature reports delirium overshadows dementia when they are comorbid [35,37].

In addition, using regression analysis for longitudinal data we found that disturbances of sleep-wake cycle were predictive of delirium rather than the other neuropsychiatric disturbances, depression, and dementia. Notably, there is a limited longitudinal literature of examining delirium features and we found that delirium was the single significant factor associated with such disturbances over time using GEE analysis. In contrast, self-rated sleep on the RCSQ did not correlate with DRS-R98 ratings either in patients with or without active delirium.

We found little correlation between the DRS-R98 sleep item and the RCSQ. These two scales differ in a number of aspects. The DRS-R98 is typically clinician-rated for sleep-wake cycle abnormalities using medical terminology, according to all available sources of information from the previous 24 hours and captures the severity of sleep-wake cycle disturbances that are characteristic of delirium. It is also anchored with text descriptions of deliriums' sleep presentations and hence more reliable than subjective reports of sleep quality. In contrast, the RCSQ is subjectively rated by the patient according to their perceptions of sleep quality during the previous night. In addition, the DRS-R98 focuses on sleep-wake cycle integrity whereas the RCSQ focuses on a variety of characteristics that include difficulty falling asleep, perceived depth of sleep, and subjective quality of the sleep experience. It is well documented that substantial differences can exist between the observed and retrospectively subjective reporting of sleep quality.

Moreover, the presence of significant cognitive impairment in a substantial percentage of our subjects is also likely to have impacted the accuracy and reliability of self-reported sleep quality [38,39]. This is congruent with other work indicating little association between daily observer rated assessments of sleep quality using RCSQ and the transition to delirium [40]. Indeed, our findings support other studies suggesting that the presence of delirium precludes the use of the RCSQ [41].

When the predictive relationship of clinician-rated sleep-wake cycle disturbance on DRS-R98 item #1 for episodes of DSM-5 diagnosed delirium was explored, it was found that a cutoff ≥ 1 (indicating at least mild forms of sleep disturbance) had a sensitivity of 80% and a specificity of 74%, suggesting that while delirium potential is detected, it is likely confounded by other reasons for mild sleep disturbance. The PPV (66%) and NPV (74%) were moderately high, although not enough to suggest that the presence of mild disturbances is sufficient to be relied on solely in clinical situations. Using a cutoff ≥ 2, sensitivity remained fairly high (77%) and specificity increased to 92%. However, the PPV decreased to 52%, although the NPV increased to 79%. Given the poor detection of delirium in real world clinical practice [42], these findings highlight the potential usefulness of including a simple assessment of sleep disturbances to augment efforts to identify possible delirium. This is particularly relevant because sleep disturbances are not generally included in commonly used screening tools for delirium such as the confusion assessment method (CAM) [43] and Nursing Delirium screening Scale (NudESC) [44]. In contrast, the Delirium Diagnostic Test-Provisional [45] used only three items—vigilance, comprehension, and the sleep-wake cycle from the DRS-R98—to provisionally diagnose delirium with a very high (97%) concordance

with DSM-IV. Furthermore, the presence of comorbid dementia in our study did not dilute the association of sleep-wake cycle disturbance with delirium. Also, recent reports investigating melatonin and related medications suggest an important role for sleep-wake circadian rhythm as a core domain feature in delirium [46,47].

In summary, we found that moderate disturbances of sleep-wake cycle were significantly different between delirium-only patients diagnosed independently of DRS-R98 ratings, irrespective of comorbid dementia status. A significant difference was also found between incident and prevalent delirium subgroups with regards to moderate sleep-wake cycle disturbances. This finding suggests that moderate or greater sleep-wake disturbances occur as delirium becomes more established rather than as an early sign of emerging incident delirium.

5. Study limitations and recommendations

There are a number of limitations to this study. Sleep ratings using the DRS-R98 were conducted during the working day and incorporated nursing and family observations from the previous 24 hours. More continuous monitoring using objective measurements such as actigraphy or polysomnography might identify changes earlier, although would be impractical in clinical situations. Previous work found a strong relationship between accelerometer patterns and DRS-R98 motor activity items, suggesting that ratings for more than a 24-hour period have high accuracy with the DRS-R98 item ratings [25].

We diagnosed dementia but did not have information about dementia type that may have affected our findings. However, given its prevalence we expect that Alzheimer's was the more common cause. It is also difficult in general hospital settings with acutely medically ill patients to focus deeply on the specific nature of a chronic disease process, and where delirium is the neuropsychiatric emergency.

In addition, we studied proportionately fewer incident cases than prevalent delirium cases such that future work might instead focus on incident cases and reasons why sleep-wake cycle disturbances may be worse in prevalent delirium. Prior longitudinal work describing graphic symptom patterns over time (using GEE) between persistent versus resolving delirium found no significant difference for DRS-R98 item #1 [23].

We tried to evaluate the role of depression as a contributor or confounder with sleep disturbances in delirium but had too few cases to analyze meaningfully. Although this study accounted for confounding factors such as medication, age, sex, comorbid depression and dementia using the GEE method, other potential confounding factors such as noise, light exposure, and social zeitgebers were not accounted for. Future work should examine the impact of these additional and potential confounding factors on sleep in particular in elderly medical admissions with cognitive impairment. Future work would also aim at more detailed longitudinal (e.g., months and years) exploration of the effects of chronic or more enduring conditions such as depression and dementia on sleep, as well as the effects of state conditions such as delirium. A final limitation of this study may be the generalizability of our findings to other clinical groups. Future work should also aim to explore the relationship between sleep and delirium in other acute clinical cohorts such as elderly postoperative patients.

6. Conclusions

Sleep disturbances are extremely common among older hospitalized patients. However, more severe disturbances that reflect circadian fragmentation and sleep-wake cycle reversal are indicative of delirium and should be carefully considered in general hospital settings even when older patients have pre-existing dementia. Clinician-observed measures of sleep-wake cycle integrity are more meaningful than subjective sleep quality reports in terms of indicating neurocognitive disorder.

RESEARCH IN CONTEXT

1. Systematic review: This article is based on the multidisciplinary approach to dementia-delirium and elder care medicine. As such, it integrates several aspects of the literature. Its theoretical framework is a mixture of clinical-based phenomenological profiling, fundamental sciences such as neuroscience, and specialty clinical fields such as liaison/elder care psychiatry and psychogeriatrics.
2. Interpretation: The key finding of this article is to highlight the utility of different methods of detecting sleep disturbances in mixed neuropsychiatric populations such as elderly medical inpatients.
3. Future directions: Future research can build on this initial study and advance it to include other modalities such as actigraphy. It can also be used to reframe approaches to phenomenological profiling of delirium and dementia.

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